Immediate versus early non-occlusal loading of dental implants placed flapless in partially edentulous patients: A 3-year randomized clinical trial


Abstract

Aim: To compare immediate versus early non-occlusal loading of dental implants placed flapless in a 3-year, parallel group, randomized clinical trial.

Materials and Methods: The study was conducted in a private dental clinic between July 2005 and July 2010. Patients 18 years or older were randomized to receive implants for fixed partial dentures in cases of partial edentulism. The test group was represented by immediate non-occlusal implant loading, whereas the control group was represented by early non-occlusal implant loading. The outcome variables were implant failure, complications and radiographic bone level at implant sites 3 years after loading, measured from the implant–abutment junction to the most coronal point of bone-to-implant contact. Randomization was computer-generated with allocation concealment by opaque sequentially numbered sealed envelopes, and the measurer was blinded to group assignment.

Results: Sixty patients were randomized: 30 to the immediately loaded group and 30 to the early loaded group. Four patients dropped out; however, the data of all patients were included in the analysis. No implant failure occurred. Two complications occurred in the control group and one in the test group. The mean bone level at 3 years was 1.91 mm for test group and 1.59 mm for control group. The adjusted difference in bone level was 0.26 mm (CI 95% –0.08 to 0.59, p = 0.1232).

Conclusion: The null hypothesis of no difference in failure rates, complications and bone level between implants that were loaded immediately or early at 3 years cannot be rejected in this randomized clinical trial.

Conflict of interest and source of funding statement
Partial support for this study was provided by Thommen Medical AG, Waldenburg, Switzerland. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors declare that there is no conflict of interest in this study.

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Traditionally, osseointegrated dental implants were submerged and kept load-free for 3–8 months to minimize the risk of implant failures (Bränemark et al. 1977). It would be beneficial to reduce the healing period without jeopardizing implant success,
Materials and Methods

This was a mono-centre, single-blind, parallel randomized clinical trial with balanced randomization (1:1) conducted in a private clinic in Rimini (Italy) between July 2005 and July 2010. The study characteristics and technical details were described in a previous article (Merli et al. 2008a). The research was conducted in full accordance with ethical principles, including the Declaration of Helsinki, and each participant gave a written consent according to the above mentioned principles.

This superiority trial tested the null hypothesis of no difference in failure rate, complications and bone level between immediate and early non-occlusal loading of dental implants for fixed partial dentures in partially edentulous patients.

In summary, eligible participants were all adults, aged 18 or over, partially dentate requiring dental implants. The implant site should allow for the placement of at least one 9.5 mm long implant, and the bone thickness at the implant site had to be at least 5.5 mm. For patients with multiple areas to be restored, the operator was free at the screening visit to select one area to be included in the trial. In this area, multiple neighbouring implants could be placed.

Exclusion criteria were: general contraindications to implant surgery, patients irradiated in the head and neck area within a year prior to surgery, patients with poor oral hygiene (full-mouth plaque score ≥ 30) and lack of motivation, uncontrolled diabetes (diabetes that is not being treated at all, or is not being adequately treated), pregnancy and lactating period, substance abusers, psychiatric problems, lack of opposing occluding dentition in the area intended for implant placement, severe bruxism or clenching, active infection or severe inflammation in the area intended for implant placement, the presence of ≤ 4 mm of keratinized mucosa and/or the need for bone augmentation procedures, with the exception of post-extractive sites treated with Bio-Oss® granules (Geistlich Biomaterials, Wolhusen, Switzerland).

One experienced surgeon (M. Merli) performed all the operations, whereas patients were restored by four restorative dentists.

Threaded cylindrical titanium implants (ELEMENT, Thommen Medical, Waldenburg, Switzerland) with a sand-blasted acid-etched surface were used. In some of the post-extraction sites, tapered CONTACT (Thommen Medical) implants were used. A flapless procedure was used (Merli et al. 2008a, b).

The objective was to reach a minimum torque of 40 N cm upon implant insertion. Implants with an insertion torque of < 40 N cm could be replaced by a larger diameter implant. Alternatively, the surgeon had the following options: to prepare another implant site; to leave the implant to heal unrestored for 6 weeks following the same procedures of early loading group; to heal unrestored for 6–8 months following the procedure of conventionally loaded implants; or to load the implant. An intention-to-treat analysis was used in these situations, and a per-protocol analysis was performed as a sensitivity analysis.

In general, implants were placed at the crestal level in healed edentulous ridges and 1 mm subcrestally in immediate post-extraction sockets. When a residual gap was present between the implant surface and the bone wall in the immediate extraction site, the gap was filled with Bio-Oss 0.25–1 mm granules. No other type of bone-grafting material was used. A non-submerged technique was followed.

Before abutment placement, the envelope containing the randomization code was opened, instructing the surgeon as to whether the procedure would involve immediate or early loading or not. Impression copings or healing abutments were placed accordingly (Merli et al. 2008a).

All provisional restorations of the immediate loaded group were placed within 72 h of implant placement. The occlusal surface of the provisional restoration was ground to avoid any occlusal contact with the opposite dentition in static and dynamic analyses.

For patients in the early loading group, impressions were taken approximately 6 weeks after implant placement. They received non-occlusally provisional fixed restorations, identical to those of the immediately loaded group.

Intra-oral radiographs of the study implant were made at implant placement and at 3 years of follow-up. Six months after implant placement, final occluding metal-porcelain restorations were applied. All patients were recalled every 3-months for oral hygiene maintenance and prosthetic controls up to the third year after implant placement.

Outcome measures evaluated in the present study at 3 years follow-up were:

1. Prosthesis failure: the prosthesis could not be placed or was lost because of implant failure.
2. Implant failure: the presence of any mobility of the individual implant and/or any situation dictating implant removal.
3 Any biological or prosthetic complications defined as unexpected deviations from the normal treatment outcome: examples of biological complications are haemorrhaging during and after implant placement and/or peri-implantitis. Peri-implantitis is defined as a marginal bone loss of 3 mm or more in combination with bleeding on probing or pus or both (Roos-Jansåker et al. 2006). Prosthetic complications included fracture of the implant or fracture of the prosthesis.

4 Peri-implant marginal bone level: periapical intra-oral radiographs were taken with the parallel technique. The digitized radiographs were examined using commercially available software (Immagine® Dental Trey srl, Fiumanapredappio FC, Italy) by an operator (G. Mariotti) blind to the group assignment. The measurer was calibrated and subjected to an intra-rater agreement test. The variable bone level at 3 years was registered. The radiographic measurement was taken from the implant–abutment junction to the most coronal point of bone-to-implant contact. The measurements were made parallel to the long axis of the implant fixture, and were made in pixels and converted to millimetres using the known length of the implant. Measurements of the mesial and distal bone crest level adjacent to each implant were made to the nearest 0.01 mm.

The sample size calculation was performed on the number of patients likely to have at least one implant failure. From a study on partially edentulous patients, the proportion of failure in the immediate loaded group was 0.39 compared with 0.04 in the conventional loaded group (Ottoni et al. 2005). A two-group continuity-corrected chi-square test with a 0.05 two-side significance level have an 80% power to detect the difference between a proportion of 0.39 and a proportion of 0.04 (odds ratio of 0.065) when the sample size in each group is of 26 patients. Thirty patients were to be included in each group to compensate for possible drop-outs.

An investigator (M. Esposito), not involved in the selection and treatment of the patients, randomly assigned participants following simple randomization procedures (computerized random numbers) to one of two treatment groups. The randomized codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes.

Envelopes were opened sequentially only after the implants to be included in the trial were inserted, and therefore treatment allocation was concealed to the investigator in charge of enrolling and treating the patients included in the trial.

Although patients and the surgeon were aware of the allocated arm, radiographic outcome assessor (G. Mariotti) was kept blinded to the allocation. Prosthesis failure, implant failure and complications were assessed by an independent assessor (M. Moscatelli), who was not blinded to the intervention.

Statistical analysis

Descriptive statistics were performed using mean (standard deviations) for quantitative data, and frequency and percentage for qualitative data.

In prosthetic failure, implant failure and complication analyses, the patient was the statistical unit. Difference in proportion between groups was compared using Fisher exact tests.

For the radiographic analysis, an intra-rater agreement was carried out. An a-priori independent sample of 24 measured implant surfaces was measured twice, 2-weeks apart. A two way intra-class correlation coefficient was calculated.

A random intercept multilevel linear model was performed with the treatment (immediate versus early loading) and post-extractive site (immediate versus delayed placement) as explicative variables. An interaction term between treatment and post-extractive implants was allowed, but if not significant, was dropped out from the model. The method used for the estimation was the iterative generalized least square (IGLS).

The two levels of the model were the patient and the surface of the implants (for example mesial and distal). The outcome variable was the bone level at 3 years.

Estimates for the treatment effect, standard errors, p-values and 95% confidence intervals were provided.

The statistical software was MLwiN (version 2.21, Centre for Multilevel Modelling, University of Bristol, Bristol, UK). Significance was set at $\alpha = 0.05$. Residual graphical analysis was performed to verify the plausibility of the key assumptions of the model as normality and homoscedasticity.

Intention-to-treat analyses were performed. If a patient dropped out at 3 years, but the data were available at 1 year, these data were used in the analyses with the logic of “last observation carried forward” (Moher et al. 2010). In any event, sensitivity per-protocol analyses were undertaken to compare the results obtained with the intention-to-treat analyses.

Results

Sixty patients were consecutively enrolled in the trial and randomized: 30 to the immediately loaded group and 30 to the early loaded group. One patient belonging to the test group and three patients belonging to the control group dropped out at 3 years. One patient dropped out due to non-planned hospitalization and illness resulting in the inability to keep further appointments in the test group and one drop-out in the control group was due to the death of the patient. Two patients in the control group dropped out due to job relocation.

Deviations from the operative protocol were described in the previous publication (Merli et al. 2008a) and can be summarized as follows: nine implants in nine patients did not obtain the planned primary stability. Five implants were in the immediate loaded group. Two of these implants were loaded immediately with a torque of 30 N cm. Of the other three implants, one was loaded early and the other two implants were conventionally loaded (one of which was placed in a patient with two other implants that were immediately loaded). Four of the implants that did not obtain the planned primary stability were loaded early, as indicated, using protocol, in the envelope.

Two implants in two patients of the early loaded group were immediately loaded (protocol deviation) and five implants in five patients of the early loaded group were conventionally
No prosthesis or implant failed. Two complications occurred in the control group and one in the test group. They were described in the previous publication (Merli et al. 2008a). No complications occurred between 1 year and 3 years after loading. There were no statistically significant differences for complications between the two procedures at 3 years ($p = 1.0$).

The two way intra-class correlation coefficient for radiographic intra-rater agreement analysis was 0.93, considered excellent (Fleiss 1986).

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The two way intra-class correlation coefficient for radiographic intra-rater agreement analysis was 0.93, considered excellent (Fleiss 1986).

The descriptive statistics for radiographic bone level at baseline and 3 years are presented in Table 2.

Baseline assessment of bone level was not available for four implants in the test group and three implants in the control group. Bone level assessment at 3-years was not available for one implant in the test group and for three implants in the control group due to the four patients who dropped out. In these cases, the 1-year radiographic data were available and was utilized in the analysis. The mean bone level was 1.91 (0.72) mm for the test group and 1.59 (0.76) mm for the control group at 3 years.

Estimates for the treatment effect, standard errors and $p$-values for the multilevel model in the intention-to-treat analysis on 60 patients (all 69 implants) are shown in Table 3. The interaction term was not significant and was therefore dropped out from the model. In the residual analysis, no deviations from assumptions of the model were shown.

The adjusted difference in bone level between treatments was

Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate $n = 30$</th>
<th>Early $n = 30$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>50.3 (28–72)</td>
<td>48.7 (19–68)</td>
</tr>
<tr>
<td>Smokers (at least 1 cigarette per day)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients receiving one implant</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Number of patients receiving two implants</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients receiving three implants</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total number of placed implants</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Implants placed in fresh extraction socket</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Immediate extraction site treated with Bio-Oss</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Implant inserted in mandibles</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Implant inserted in anterior area (canine to canine)</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Radiographic characteristics (bone level in mm) of implant surface: mesial and distal for each implant. Mean (standard deviation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone level baseline (mm)</td>
<td>3.51 (1.78)</td>
<td>3.13 (1.72)</td>
</tr>
<tr>
<td>Bone level 3 years (mm)</td>
<td>1.91 (0.72)</td>
<td>1.59 (0.76)</td>
</tr>
</tbody>
</table>

Table 3. Multilevel model in the intention-to-treat analysis for bone level at 3 years of follow-up. Model: Bone level: $b_{0ij} + b_{1ij}$ Treatment + $b_{2ij}$ Post-extractive site

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Standard error</th>
<th>$p$-value error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.98</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>0.26</td>
<td>0.17</td>
<td>0.1232</td>
</tr>
<tr>
<td>Post-extractive site</td>
<td>-0.20</td>
<td>0.16</td>
<td>0.2096</td>
</tr>
<tr>
<td>$\sigma^2_u$</td>
<td>0.31</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_e$</td>
<td>0.23</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

$\sigma^2_u$ and $\sigma^2_e$ are the variances at patient and site level respectively.

Intercept is a random coefficient. Treatment assumes the value 1 if the implant was from the immediate (test) group and 0 if the implant was from the early (control) group. Post-extractive site assumes the value 1 in case of post-extractive implant and 0 in case of non-post-extractive implants.

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The control group had a better result (a lower bone level) with respect to the test group, but this difference is not statistically significant ($p = 0.1232$). The adjusted difference in bone level between post-extractive and non-post-extractive implants was $-0.20$ mm (CI 95% from $-0.52$ to $0.12$). The post-extractive sites had better results (a lower bone level) with respect to non-post-extractive sites, but this difference is not statistically significant ($p = 0.2096$).

In the sensitivity per-protocol analysis, conducted on the 49 patients (27 patients with 31 implants in the test group and 22 patients with 26 implants in the control group) utilizing only the implants loaded in the prescribed way and patients visited at the 3 year follow-up, the difference in adjusted bone level between treatments was $0.34$ mm (CI 95% from $-0.04$ to $0.73$, $p = 0.0717$). The result of this analysis was substantially the same as the intention-to-treat analysis.

A test group case and a control group case are shown in Figs 2 and 3.

**Discussion**

The objective of this 3-year parallel randomized clinical trial was to compare implant failure, prosthetic failure, complications and radiographic bone level of immediate (test) versus early (control) non-occlusal loading of dental implants. There were no implant failures or prosthetic failures, and there were only three minor complications.

With regard to the radiographic bone level at 3-years, there were no differences between immediate and early loaded implants. These results are in accordance with the findings of the other published RCTs (Cannizzaro et al. 2008a, b, c, Ganeles et al. 2008, Capelli et al. 2010). It is likely that a significant difference in clinical and radiological outcome between these two types of loading does not exist (Esposito et al. 2009, Atieh et al. 2010). Another study found that immediate loaded implants in the posterior mandible were associated with a lower survival rate with respect to early loaded implants, although marginal bone levels were not different at 3 years (Zembic et al. 2010). Nevertheless, three studies consider implants inserted raising a flap (Ganeles et al. 2008, Capelli et al. 2010, Zembic et al. 2010) and three studies consider implants inserted using a flapless technique, but with completely different clinical conditions from those in this study. In fact, they consider mandibular bar-retained overdentures, implant supported maxillary full-arch prostheses or 7-mm long single implants (Cannizzaro et al. 2008a, b, c).
The implant bone level at 3-years was favourable when compared with baseline level. In this study, 29 implants were placed in fresh extraction sockets, where a marginal bone defect was frequently present at baseline. At the 3-year follow-up, the favourable implant bone level may be related to the healing process of the initial bone defect and to the characteristics of the implant surface. A mean bone level of 1.5–2.0 mm at follow-up is frequently confirmed in literature for immediate and early loaded implants (Ganeles et al. 2008, Zembic et al. 2010, Van de Velde et al. 2010).

A limit to this study is represented by the deviation from the protocol. The statistical analysis of this RCT was intention-to-treat, and the data were analysed on a random basis (Moher et al. 2010). It is important to point out that a few patients, due to work commitments, health problems and/or financial reasons, etc., were unable to follow the designed protocol completely. A sensitivity per-protocol analysis was performed only on the implants loaded in the prescribed way with the 3-year radiographic follow-up. This evaluation confirmed the results obtained in the intention-to-treat analysis.

The sample size of this study was calculated with a power analysis based on a study in which the proportion of failure in the immediate loaded group was 0.39 (Ottoni et al. 2005). However, the incidence of failure was lower than predicted and there was no implant failure. In that study, the primary stability was standardized with a minimum insertion torque of 20 N cm (Ottoni et al. 2005), whereas in this study, the objective was to reach a minimum torque of 40 N cm upon implant insertion. This fact can account for the different failure implant rate between the two studies. Hence, this study could be underpowered with regard to failure of the implants. In addition, the protocol deviation could have reduced the power of the study to detect meaningful smaller clinical differences between treatments.

This study was carried out in a private clinic, and the interventions were performed by an expert surgeon with 20 years experience in implant surgery. This should be taken into consideration when extrapolating the results from this trial to other settings.

In conclusion, the null hypothesis of no difference in failure rates, complications and bone level between implants that were loaded immediately or early at 3 years cannot be rejected in this randomized clinical trial.

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References


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Clinical Relevance

Scientific rationale for study: To reduce the healing period of implants without jeopardizing success.

Principal findings: No clinical or radiological differences were observed when comparing implants that were loaded immediately or early at the 3-year follow-up. In both test and control groups, an acceptable level of bone was observed.

Practical implications: In this specific patient population, reducing the healing time does not compromise the radiographic bone level of dental implants after 3 years of loading.